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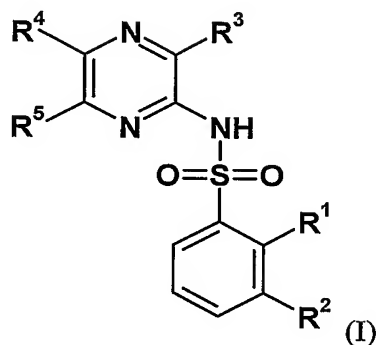
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(54) Title: NOVEL N-(FLUORO-PYRAZINYL)-PHENYLSULFONAMIDES AS MOODULATORS OF CHEMOKINE RECEPTOR CCR4.



(57) Abstract: The invention provides N-(fluoro-pyrazinyl)-phenylsulfonamides of formula (I) wherein R1 -R5 are as defined in the specification; processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy

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Novel N-(fluoro-pyrazinyl)-phenylsulfonamides as modulators
of chemokine receptor CCR4.

The present invention relates to N-(fluoro-pyrazinyl)-phenylsulfonamides, processes
and intermediates used in their preparation, pharmaceutical compositions containing them
5 and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various
diseases and disorders, including asthma and allergic diseases, as well as autoimmune
pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted
molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved
10 four cysteine motif. At the present time, the chemokine superfamily comprises three
groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C)
and Cys-X₃-Cys (C-X₃-C) families. The C-X-C and C-C families have sequence similarity
and are distinguished from one another on the basis of a single amino acid insertion
between the NH-proximal pair of cysteine residues. The C-X₃-C family is distinguished
15 from the other two families on the basis of having a triple amino acid insertion between the
NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of
neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

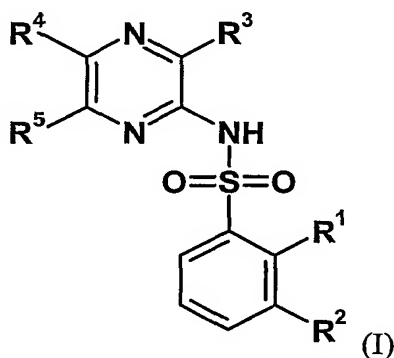
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes
20 but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1,
MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and
Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and
MIP-1 β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage
Derived Chemokine (MDC, CCL22). The C-X₃-C chemokine (also known as fractalkine)
25 is a potent chemoattractant and activator of microglia in the central nervous system (CNS)
as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of chemokines are mediated by subfamilies
of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2,
CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11
30 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C
family) and CX₃CR1 for the C-X₃-C family. These receptors represent good targets for
drug development since agents which modulate these receptors would be useful in the

treatment of disorders and diseases such as those mentioned above. Agents effective at modulating the CCR4 receptor are of particular interest for use in the treatment of inflammatory diseases.

WO 03/051870 and WO 03/059893 disclose a series of sulphonamide compounds said to be useful for treating various diseases. It has now surprisingly been found that a narrow class of compounds generically disclosed in WO 03/059893 exhibit advantageous pharmaceutical properties. For example, in addition to high potency the compounds of the present invention also exhibit low plasma protein binding to human plasma, which increases effectiveness in vivo.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R¹ is selected from methyl, chlorine and fluorine;

R² is selected from methyl, chlorine and fluorine;

R³ is methoxy;

one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is selected from hydrogen and hydroxymethyl.

Suitable pharmaceutically acceptable salts of formula (I) include include metal salts, such as an alkali metal salt (for example a sodium or potassium salt) or an alkaline earth metal salt (for example magnesium or calcium), or an organic amine salt for example ammonia, triethylamine, piperidine, piperazine or dibenzylamine.

It will be understood that certain compounds of the present invention and pharmaceutically acceptable salts thereof may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all

such solvated forms. The present invention also encompasses any tautomers of compounds of formula (I), or mixtures thereof.

In an embodiment of the invention, R¹ is selected from chlorine and fluorine, and R² is selected from chlorine and fluorine.

5 In an embodiment of the invention, R¹ is chlorine and R² is chlorine.

In an embodiment of the invention, R⁴ is fluorine and R⁵ is selected from hydrogen and hydroxymethyl.

In an embodiment of the invention, R⁵ is fluorine and R⁴ is selected from hydrogen and hydroxymethyl.

10 In an embodiment of the invention, one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is hydrogen.

In an embodiment of the invention, one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is hydroxymethyl.

In an embodiment of the invention, R⁴ is hydrogen and R⁵ is fluorine.

15 In an embodiment of the invention, R⁴ is hydroxymethyl and R⁵ is fluorine.

In an embodiment of the invention, R⁴ is fluorine and R⁵ is hydrogen.

In an embodiment of the invention, R⁴ is fluorine and R⁵ is hydroxymethyl.

In an embodiment of the present invention the compound of formula (I) is selected from:

20 2-Chloro-3-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-(6-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-[6-fluoro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]-benzenesulfonamide,

25 3-Chloro-2-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-[5-fluoro-6-(hydroxymethyl)-3-methoxypyrazin-2-yl]-benzenesulfonamide,

3-Chloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-2-methyl-benzenesulfonamide,

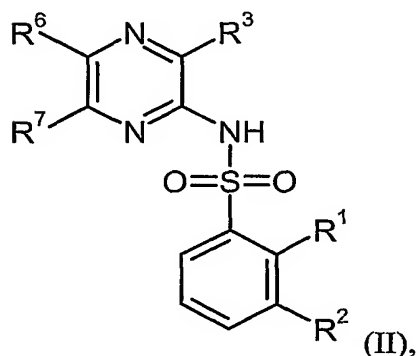
or a pharmaceutically acceptable salt thereof.

30 Pharmaceutical compounds may be metabolised to form other compounds in vivo. For *N*-pyrazinyl-phenyl sulphonamides, one type of metabolite that may be formed in vivo is an aminopyrazine derivative. Some aminopyrazine derivatives display mutagenicity, i.e.

they are AMES +ve according to the test procedure of Maron and Ames described in Mutation Res. 1983; 113:173-215. It is a further advantage of the compounds of the present invention that their aminopyrazine derivatives are not mutagenic.

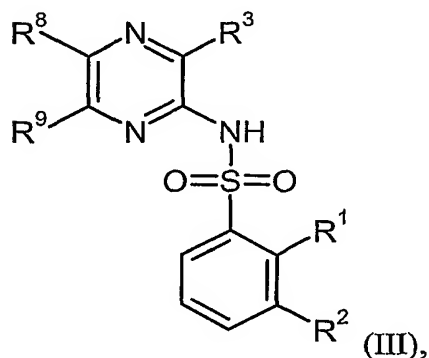
According to the present invention there is also provided a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises

(a) reacting a compound of formula (II), wherein R^1 , R^2 and R^3 are as defined in formula (I) and one of R^6 and R^7 is hydrogen and the other of R^6 and R^7 is NH_2 , with a nitrite salt in the presence of a fluorinating agent,



or

(b) reacting a compound of formula (III), wherein R^1 , R^2 and R^3 are as defined in formula (I) and one of R^8 and R^9 is fluorine and the other of R^8 and R^9 is bromine, with hydrogen in the presence of a palladium catalyst,

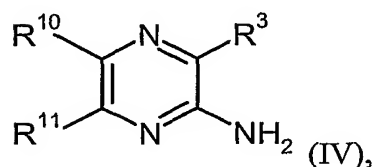


or

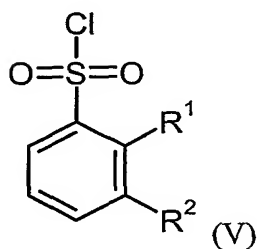
(c) where one of R^4 and R^5 is hydroxymethyl, reacting a compound of formula (III) as described in (b), with carbon monoxide in the presence of a palladium catalyst, and

subsequently treating the resulting acid (or C₁₋₄ alkyl ester thereof) with a suitable reducing agent, or

(d) where one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is hydrogen, reacting a compound of formula (IV), wherein R³ is as defined in formula (I) and where one of R¹⁰ and R¹¹ is fluorine and the other of R¹⁰ and R¹¹ is hydrogen,

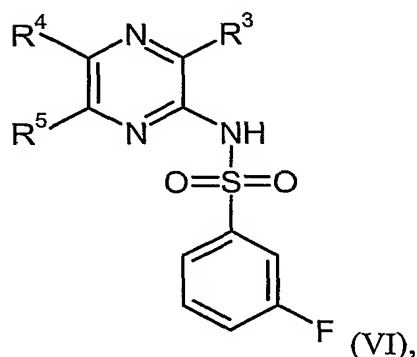


with a compound of formula (V), wherein R¹ and R² are as defined in formula (I)



or

(e) where R² is fluorine and R¹ is chlorine, reacting a compound of formula (VI) wherein R³, R⁴ and R⁵ are as defined in formula (I), with hexachloroethane in the presence of a lithium amide or alkyl lithium base,



and optionally after (a), (b), (c), (d) or (e) carrying out one or more of the following:

- converting the compound to a further compound of the invention or

- forming a pharmaceutically acceptable salt of the compound.

It will be understood by those skilled in the art that in compounds of formula (II) the hydrogen atom that is located at R⁶ or R⁷ will not undergo transformation in process (a) and will be the hydrogen atom at either R⁴ or R⁵ in the resulting compound of formula (I).

5 Similarly, in compounds of formula (III) the fluorine atom that is located at R⁸ or R⁹ will not undergo transformation in process (b) and will be the fluorine atom at either R⁴ or R⁵ in the resulting compound of formula (I). In compounds of formula (IV), the substituents at R¹⁰ and R¹¹ will not undergo transformation in process (d) and they correspond directly with the substituents at R⁴ or R⁵ in the resulting compound of formula (I).

10 In process (a) the reaction may be performed in a solvent such as acetonitrile, at a temperature in the range of -10°C to 50 °C. The nitrite salt may be sodium nitrite (either in the form of an aqueous solution or solid) and the fluorinating agent may for example be tetrafluoroboric acid or hydrogen-fluoride in pyridine.

In process (b) the reaction may be performed in a suitable solvent such as ethyl acetate
15 at a hydrogen pressure of, for example, 1 bar, in the presence of a suitable base such as triethylamine and a palladium catalyst such as 5% Pd on charcoal, at a temperature in the range of 0 to 50 °C.

In process (c) the initial reaction may be performed in a suitable solvent such as methanol, ethanol at a carbon monoxide pressure of, for example, 3-7 bar, in the presence
20 of a suitable tertiary amine base such as triethylamine or diisopropylethylamine and a suitable palladium catalyst such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, and at a temperature in the range of 70 to 100°C. When performed in the presence of an alcohol solvent the resulting acid will be converted to the corresponding alkyl ester, e.g. the methyl
25 ester will be formed when methanol is the solvent. The reaction may also be performed in a solvent such as dimethylformamide, in which case the acid will be obtained. Subsequent reduction of the alkyl ester to the alcohol may be performed in a suitable solvent such as tetrahydrofuran using a suitable reducing agent such as lithium triethylborohydride at a temperature in the range of 0 to 30°C. Reduction of the acid to the alcohol may be achieved
30 using conventional chemistry.

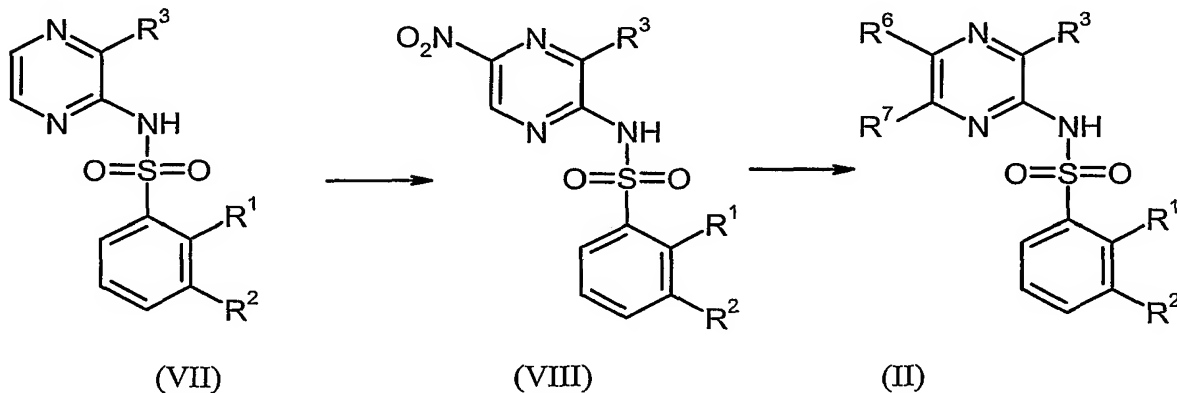
In process (d) the reaction may be performed in a suitable solvent such as 1,2-dimethoxyethane or tetrahydrofuran, at a temperature in the range of 0 to 50 °C, under the influence of a base such as NaH or potassium tert-butoxide.

In process (e) the reaction may be performed in suitable solvent such as tetrahydrofuran or hexane or mixtures thereof, by treatment with a suitable base such as lithium diisopropylamide, followed by the addition of hexachloroethane, at a temperature in the range of -78 to 0°C.

Compounds of formulae (II), (III) or (V) are either commercially available, are known in the literature or may be prepared using known techniques. Examples of preparation methods for certain of these compounds are given hereinafter in the examples. Other

For example, compounds of formula (II) wherein R⁶ is NH₂ and R⁷ is hydrogen may be prepared according to Scheme 1, wherein R¹, R² and R³ are as defined in formula (I).

Scheme 1

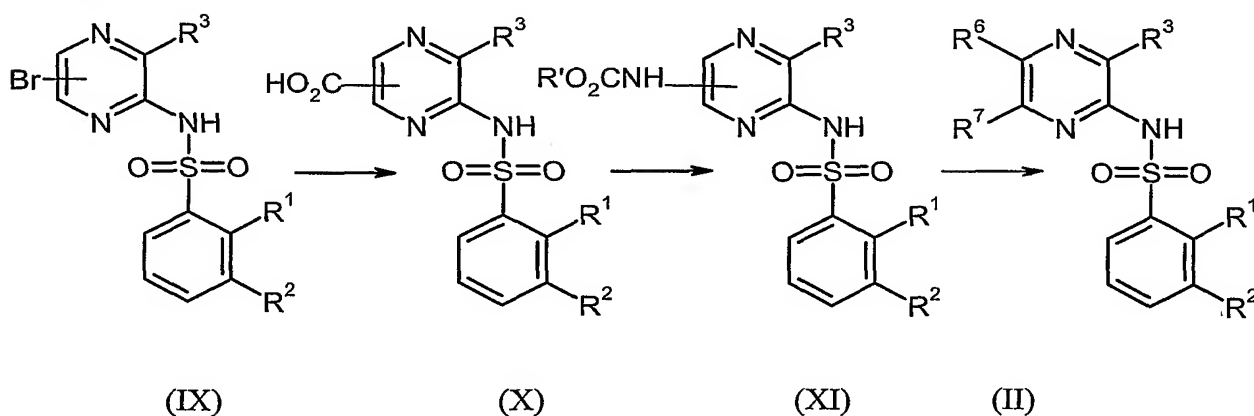


According to Scheme 1, compounds of formula (VII) are converted to compounds of formula (VIII) by reacting (VII) with fuming nitric acid in a suitable solvent such as acetic acid at a temperature of from 50 to 100°C, or alternatively reacting (VII) with nitronium tetrafluoroborate in a suitable solvent such as acetonitrile or sulfolane at a temperature of from 0 to 50 °C. Subsequently, (VIII) is converted to a compound of formula (II) wherein R⁶ is NH₂ and R⁷ is hydrogen, by hydrogenation (1-3 bar) in a suitable solvent such as acetic acid or acetic acid/ethyl acetate mixtures with a suitable hydrogenation catalyst such as 5-10% palladium on charcoal at a temperature of from 20 to 70°C, or alternatively by reacting (VIII) with a metal such as iron powder in a suitable solvent such as ethyl acetate

containing concentrated hydrochloric acid heated at a temperature of from 50 to 100°C. Compounds of formula (VII) may be prepared by methods according or analogous to those described in WO03/059893.

Alternatively, compounds of formula (II) may be prepared according to Scheme 2,
 5 wherein R¹, R² and R³ are as defined in formula (I).

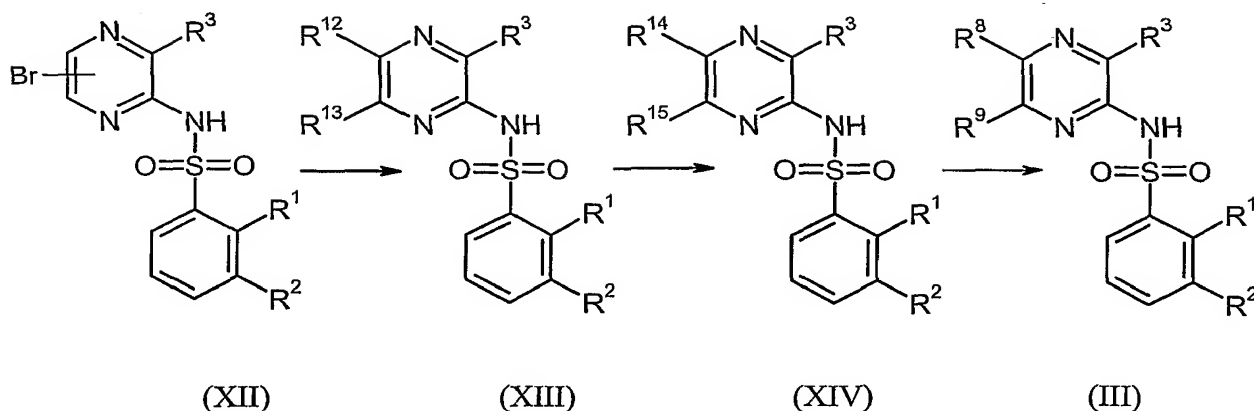
Scheme 2



According to Scheme 2, (IX) is converted to (X) by reacting (IX) with carbon monoxide (3-7 bar) in a suitable solvent such as methanol in the presence of a suitable tertiary amine base such as triethylamine or diisopropylethylamine and suitable palladium catalyst such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane at a temperature of from 60 to 100°C, followed by hydrolysis of the methyl ester to yield (X). (X) is converted to carbamate (XI) by reacting (X) with diphenylphosphoryl azide and para methoxybenzyl alcohol or tertiary butanol, in the presence of a suitable amine base such as triethylamine in a suitable solvent such as tetrahydrofuran heated to reflux. Carbamate (XI) is converted to (II) by treatment with a suitable acid such as HCl (e.g. 4M) in dioxane. Compounds of formula (IX) may be prepared by methods according or analogous to those described in WO03/059893.

Compounds of formula (III) may, for example, be prepared by as depicted in Scheme 3, wherein R¹, R² and R³ are as defined in formula (I).

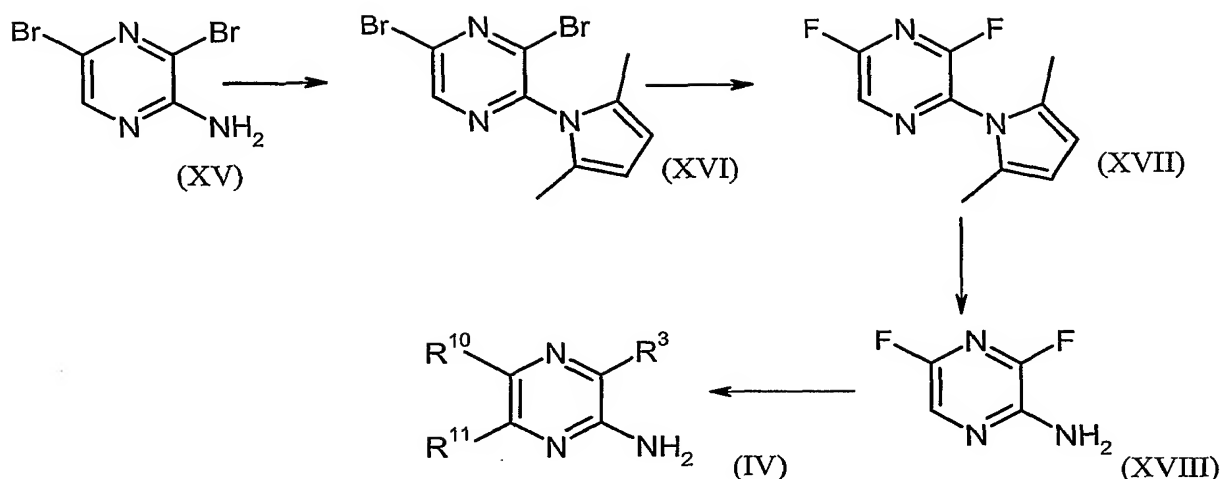
Scheme 3



According to Scheme 3, compounds of formula (XII) are converted to compounds of formula (XIII), wherein one of R^{12} and R^{13} is NO_2 and the other of R^{12} and R^{13} is bromine, by reacting (XII) with fuming nitric acid in a suitable solvent such as acetic acid at a temperature of from 50 to 100°C , or alternatively reacting (XII) with nitronium tetrafluoroborate in a suitable solvent such as acetonitrile or sulfolane at a temperature of from 0 to 50°C . Subsequently, (XIII) is converted to (XIV), wherein one of R^{14} and R^{15} is NH_2 and the other of R^{14} and R^{15} is bromine, by hydrogenation (1-3 bar) in a suitable solvent such as acetic acid or acetic acid/ethyl acetate mixtures with a suitable hydrogenation catalyst such as 5-10% palladium on charcoal at a temperature of from 20 to 70°C , or alternatively by treating (XIII) with a metal such as iron powder in a suitable solvent such as ethyl acetate containing concentrated hydrochloric acid heated at a temperature of from 50 to 100°C . (XIV) may then be converted into (III) by reacting (XIV) with a nitrite salt in the presence of fluorinating agent in an analogous method to that described in process (a) herein above. Compounds of formula (XII) may be prepared by methods according or analogous to those described in WO03/059893.

Compounds of formula (IV) wherein R^{10} is fluorine and R^{11} is hydrogen may be prepared as depicted in Scheme 4.

Scheme 4



According to Scheme 4, compound (XV) is converted to (XVI) by reacting (XV) with acetylacetone in the presence of para-toluenesulfonic acid in a suitable solvent such as toluene at a temperature of from 80 to 110°C. (XVI) is then converted to (XVII) by reaction of (XVI) with potassium fluoride in the presence of 18-crown-6 in a suitable solvent such as 2-methoxyethyl ether at a temperature of from 100 to 130°C. Treating (XVII) with hydrochloric acid in water and a suitable solvent such as dioxane at a temperature of from 40 to 60°C yields (XVIII), which is converted to a compound of formula (IV), wherein R¹⁰ is fluorine and R¹¹ is hydrogen, by reacting (XVIII) with sodium methoxide in methanol at a temperature of from 0 to 30 °C. Compounds of formula (IV) wherein R¹¹ is fluorine and R¹⁰ is hydrogen may be prepared by analogous chemistry.

Intermediate compounds of formula (IV) have not been prepared previously. Accordingly, in a further aspect the present invention further provides a compound of formula (IV),



wherein R³ is methoxy; one of R¹⁰ and R¹¹ is fluorine and the other of R¹⁰ and R¹¹ is hydrogen. In one embodiment of the invention R¹⁰ is fluorine and R¹¹ is hydrogen. In another embodiment of the invention of R¹¹ is fluorine and R¹⁰ is hydrogen.

Compounds of formula (V) are known in the literature or may be prepared by known methods.

Compounds of formula (VI) may, for example, be prepared by analogous methods to those described herein above for the formation of compounds of formula (I).

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl, carboxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the addition/removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991) and 'Protecting Groups', P.J. Kocienski, Georg Thieme Verlag (1994).

The compounds of the invention, or pharmaceutically acceptable salts thereof, have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR4) activity. Diseases and conditions which may be treated with the compounds include:

1. *respiratory tract*: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. *bone and joints*: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;

3. *pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease*: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. *skin*: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid,

epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5 5. *eyes*: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

10 6. *gastrointestinal tract*: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

15 7. *abdominal*: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. *genitourinary*: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-

20 vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. *allograft rejection*: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. *CNS*: Alzheimer's disease and other dementing disorders including CJD and nvCJD;

25 amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including

30 diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and

peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. *cardiovascular*: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. *oncology*: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. *gastrointestinal tract*: Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention further provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use in therapy.

The compounds of the present invention may be used to treat diseases by modulating activity of a CC chemokine receptor subfamily, in particular, by modulating activity of the CCR4 receptor. Particular conditions which can be treated with the compound of the

invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the
5 manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

10 In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of the CCR4 receptor is beneficial.

In a still further aspect, the present invention provides the use of a compound of
15 formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of asthma.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease,

20 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises
25 administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention still further provides a method of treating a disease mediated by the CCR4 receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as
30 hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as asthma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

5 For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical
10 composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all
15 percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical
20 composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols
25 and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Conveniently the compound of the invention is administered orally.

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumiarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

5 The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

10 The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and
15 stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761;
20 a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

25 The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and
30 compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol,

salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine,

lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as
5 a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the
10 invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a COMT inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide
15 synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of
20 acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or
25 topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the
30 invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including

VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B1. - or B2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK1 or NK3 receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CCR2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NF κ B, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuporelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

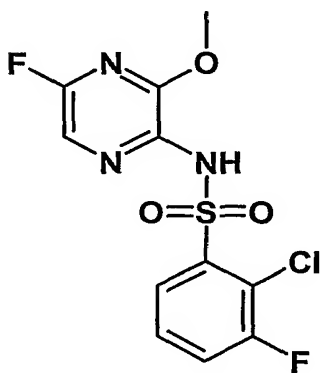
(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or

a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or
(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

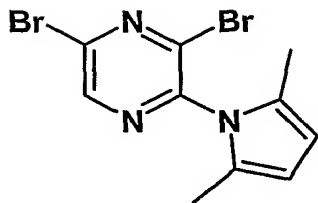
The present invention will now be further explained by reference to the following illustrative examples. In the examples the NMR spectra were measured on a Varian Unity spectrometer at a proton frequency of either 300 or 400 MHz. The MS spectra were measured on either an Agilent 1100 MSD G1946D spectrometer or a Hewlett Packard HP1100 MSD G1946A spectrometer. Preparative HPLC separations were performed using a Waters Symmetry[®] or Xterra[®] column using 0.1% aqueous trifluoroacetic acid: acetonitrile, 0.1% aqueous ammonia: acetonitrile or 0.1% ammonium acetate: acetonitrile as the eluant.

Example 1

2-Chloro-3-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)- benzenesulfonamide

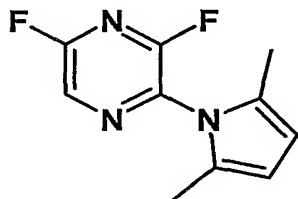


a) 3,5-Dibromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-pyrazine



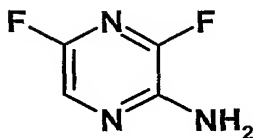
3,5-Dibromo-2-pyrazinamine (Synthesis, 1990, p659-660) (6.33g), acetonylacetone (4.42g) and p-toluenesulphonic acid (0.4g) in toluene (100ml) was heated under reflux
5 using a Dean and Stark trap. After 2h, the reaction mixture was allowed to cool, evaporated under reduced pressure to approximately 15ml. The solution was diluted with dichloromethane and passed through a silica gel column eluting with dichloromethane. After evaporation of the solvent, the product crystallised on standing. Yield 8.00g.
m/e 330/332/334 (M+1)

10 **b) 2-(2,5-dimethyl-1H-pyrrol-1-yl)-3,5-difluoro-pyrazine**



15 3,5-Dibromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-pyrazine (product from step a) (7.3g), anhydrous potassium fluoride (4.2g) and 18-crown-6 (0.2g) in anhydrous 2-methoxyethyl ether (30ml), under nitrogen were heated at 120°C for 16h. After cooling, the mixture was partitioned between water and dichloromethane. The dichloromethane solution was washed with water and then passed through a large pad of silica gel eluting with
20 dichloromethane. The solvent was evaporated to afford the product. Yield 4.5g.
1H NMR (D6-DMSO) δ 8.37 (1H, dd), 5.96 (2H, s), 2.07 (6H, s).

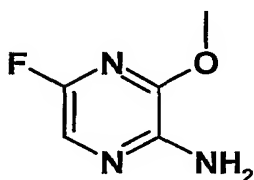
c) 3,5-Difluoro-2-pyrazinamine



2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3,5-difluoro-pyrazine (product of step b) (0.4g) in water (6ml) and HCl in dioxane (20ml of a 4M solution) was heated at 50°C for 16h. The solution was then concentrated to about 8ml and partitioned between water and ethyl acetate. The ethyl acetate layer was dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:3. The solvent was evaporated to afford the product. Yield 0.09g.

¹H NMR (CDCl₃) δ 7.77 (1H, dd), 4.70 (2H, br s).

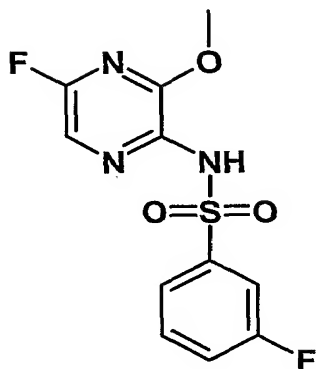
d) 5-Fluoro-3-methoxy-2-pyrazinamine



3,5-Difluoro-2-pyrazinamine (product of step c) (0.09g) and sodium methoxide (0.3ml of a 25% solution in methanol) in methanol (2ml) were stirred at room temperature. After 0.5h, the solution was partitioned between ethyl acetate and saturated aqueous ammonium chloride. The ethyl acetate layer was dried (MgSO₄) and evaporated to give the product. Yield 0.06g.

¹H NMR (CDCl₃) δ 7.37 (1H, d), 4.65 (2H, br s), 4.00 (3H, s).

e) 3-Fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide



Potassium tert-butoxide (4ml of 1M solution in tetrahydrofuran) was added dropwise to a stirred solution of 5-fluoro-3-methoxy-2-pyrazinamine (product of step d) (0.25g) and 3-fluorobenzenesulfonyl chloride (0.43g) in dry tetrahydrofuran (5ml) cooled in an ice bath. After 0.5h, the reaction mixture was quenched with 2M aqueous hydrochloric acid (50ml). The mixture was extracted with ethyl acetate. The ethyl acetate layer was dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:3. The solvent was evaporated to afford the product. Yield 0.42g.

¹H NMR (D₆-DMSO) δ 11.27 (1H, br s), 7.73-7.90 (3H, m), 7.67-7.73 (1H, m), 7.50-7.60 (1H, m), 3.92 (3H, s).

f) 2-Chloro-3-fluoro-N-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide

3-Fluoro-N-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide (product from step e)(0.19g) in dry tetrahydrofuran (3ml) was added dropwise to a stirred solution of LDA (made by adding 0.56ml of 2.5M BuLi in hexanes to diisopropylamine (0.18g)) in dry tetrahydrofuran (7ml) at -78°C. After 15 minutes, hexachloroethane (0.6g) in dry tetrahydrofuran (3ml) was added dropwise. After 1h, the cooling bath was removed and the solution allowed to warm to room temperature. The reaction mixture was partitioned between ethyl acetate and 2M aqueous hydrochloric acid. The organic layer was evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:3. The solvent was evaporated to afford the product. Yield 0.13g.

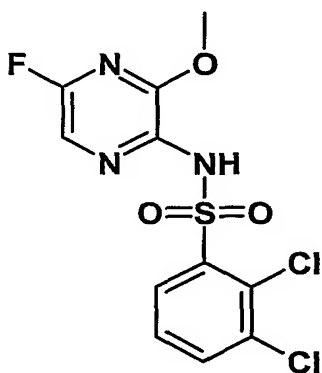
m/e 336/338 (M+1)

¹H NMR (D6-DMSO) δ 11.54 (1H, br s), 7.91 (1H, dd), 7.7-7.8 (2H, m), 7.61 (1H, dt), 3.90 (3H, s).

¹³C NMR (D6-DMSO) δ 157.9 (d, J 249 Hz), 154.7 (d, J 248 Hz), 149.4 (d, J 8.8 Hz), 140.4, 134.1 (d, J 3.6 Hz), 128.7 (d, J 8.2 Hz), 126.7 (d, J 3.2 Hz), 121.0 (d, J 21.8 Hz),
 5 118.1 (d, J 38.3), 117.8 (d, 20.4 Hz), 54.7.

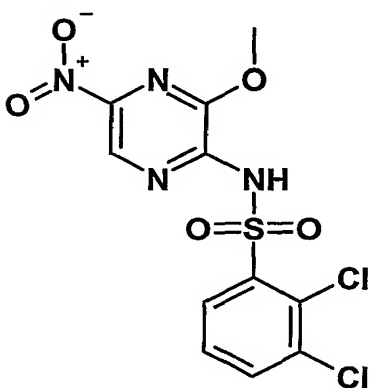
Example 2

2,3-dichloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide



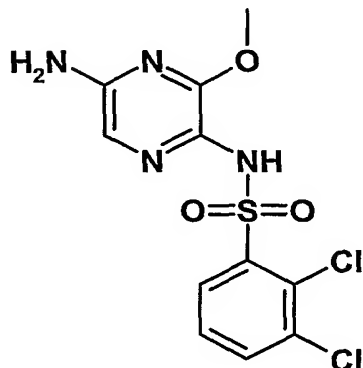
10

a) 2,3-dichloro-*N*-(3-methoxy-5-nitropyrazin-2-yl)-benzenesulfonamide



Fuming nitric acid (1.26g) was added dropwise to a stirred suspension of 2,3-dichloro-*N*-(3-methoxypyrazin-2-yl)-benzenesulfonamide (WO2003059893, example 30) (4.5g) in
 15 acetic acid (45ml) at room temperature. The reaction was carefully heated to 75°C. After 1h, the reaction mixture was allowed to cool and the white crystalline product collected by filtration. Yield 3.94g.

¹H NMR (D6-DMSO) δ 8.53 (1H, s), 8.16 (1H, d), 7.95 (1H, d), 7.61 (1H, t) 4.02 (3H, s).

b) *N*-(5-amino-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide

2,3-Dichloro-*N*-(3-methoxy-5-nitropyrazin-2-yl)-benzenesulfonamide (product of step
5 2a) (4g) and 5% palladium on charcoal (Johnson Matthey type 440 paste) (0.8g) in acetic
acid (40ml) was heated at 60°C under a hydrogen atmosphere (1 bar) until hydrogen uptake
ceased (16h). After cooling to room temperature the precipitated product and palladium
catalyst was collected by filtration and washed with a little acetic acid. The solid was
suspended in tetrahydrofuran (500ml) and stirred for 1h. The palladium catalyst was
10 removed by filtration through celite. The tetrahydrofuran solution was evaporated to
dryness and toluene added to the solid and evaporated under reduced pressure to give a
light brown solid. Yield 2.6g

¹H NMR (D6-DMSO) δ 10.04 (1H, s), 7.91-7.88 (2H, m), 7.50 (1H, t), 7.08 (1H, s), 6.43
(2H, br s), 3.59 (3H, s).

c) 2,3-dichloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)- benzenesulfonamide

Sodium nitrite (0.44g) was added portionwise to a stirred solution of
N-(5-amino-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide (product of step 2b)
20 (2g) in acetonitrile (10ml) and 48% aqueous HBF₄ (25ml) cooled in an ice bath. After 1h,
the reaction mixture was poured on to water (250ml) and extracted with ethyl acetate. The
ethyl acetate solution was evaporated to dryness and the product purified by silica gel
chromatography eluting with ethyl acetate:iso-hexanes 1:4. The solvent was evaporated to
afford the product. Yield 0.4g.

25 m/e 350/352/354 (M-1)

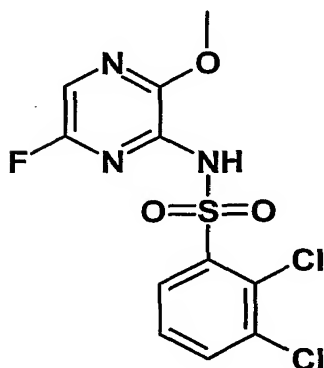
¹H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.95 (1H, dd), 7.73 (1H, d), 7.59 (1H, t), 3.90 (3H, s)

¹³C NMR (D6-DMSO) δ 154.2 (d, J 256 Hz), 149.0 (d, J 7.9 Hz), 140.3, 134.1, 133.6, 133.2, 129.4, 128.1, 127.9, 117.5 (d, J 37.5 Hz), 54.2

5

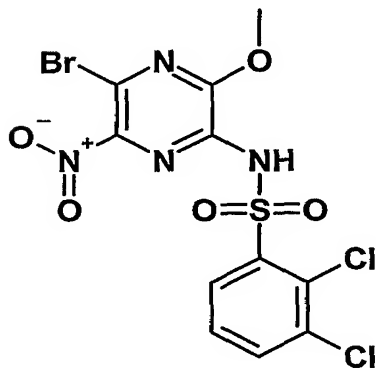
Example 3

2,3-Dichloro-*N*-(6-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide



10

a) *N*-(5-Bromo-3-methoxy-6-nitropyrazin-2-yl)-2,3-dichloro-benzenesulfonamide



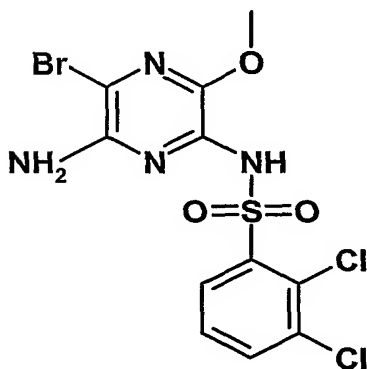
Nitronium tetrafluoroborate (7.5g) was added portionwise over about 15 minutes to a stirred suspension of *N*-(5-bromo-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide (WO2003059893, example 8) (10.0g) in acetonitrile (100ml). After 2h, further nitronium tetrafluoroborate (0.75g) was added. After a further 1h, the reaction mixture was poured on to ice/water and extracted with dichloromethane. The extracts were dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with

15

ethyl acetate:iso-hexanes 1:1. The solvent was evaporated to afford the product. Yield 8.4g.

¹H NMR (CDCl₃) δ 8.36 (1H, m), 7.74 (1H, m), 7.49 (1H, t), 4.18 (3H, s).

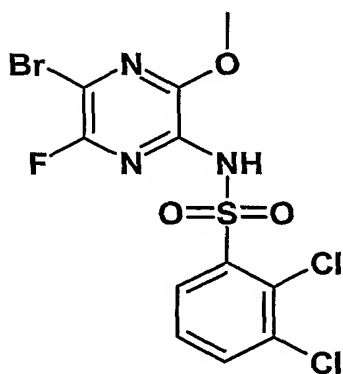
b) *N*-(6-Amino-5-bromo-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide



N-(5-Bromo-3-methoxy-6-nitropyrazin-2-yl)-2,3-dichloro-benzenesulfonamide (product of step 3a) (7.4g) in ethyl acetate (100ml) and acetic acid (50ml) containing 5% palladium on charcoal (Johnson Matthey type 39 paste) (3.2g) was put under hydrogen (1 bar) with vigorous stirring. After 3h, the reaction mixture was filtered through a pad of celite and evaporated. Yield 6.5g.

m/e 427/429 (M+1)

c) *N*-(5-Bromo-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide



Sodium nitrite (2.4g) was added portionwise over about 20 minutes to a stirred solution of *N*-(6-Amino-5-bromo-3-methoxypyrazin-2-yl)-2,3-dichloro-

benzenesulfonamide (product of step 3b) (7.4g) in hydrogen fluoride-pyridine (pyridinium poly(hydrogen fluoride)) (30ml) cooled to -10°C . After 0.5h, water was added and the solution extracted with dichloromethane (x2). The combined extracts were washed with water and then passed through a silica gel pad eluting with 1.25% methanol in dichloromethane. Purification was by silica gel chromatography eluting with methanol:dichloromethane 1:100. The solvent was evaporated to afford the product. Yield 4.1g.

m/e 430/432 (M+1)

d) 2,3-Dichloro-*N*-(6-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide

N-(5-Bromo-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide (product from step 3c) (0.2 g) in ethyl acetate (10ml) and triethylamine (1ml) containing 5% palladium on charcoal (Johnson Matthey type 39 paste) (0.4g) was put under hydrogen (1 bar) with vigorous stirring. After 0.5h, the reaction mixture was filtered through a pad of celite and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:4. The solvent was evaporated to afford the product. Yield 0.06g.

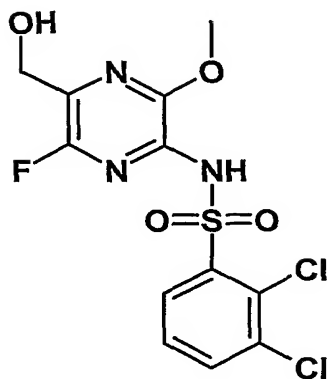
m/e 352/354/356 (M+1)

^1H NMR (D6-DMSO) δ 8.13 (1H, dd), 7.95 (1H, dd), 7.75 (1H, d), 7.62 (1H, t), 3.91 (3H, s)

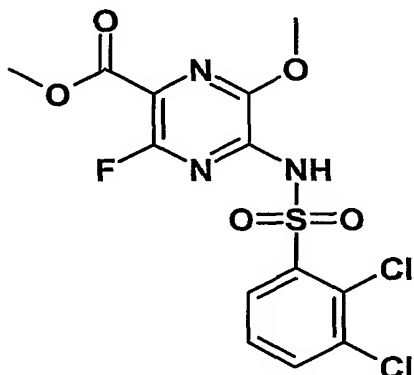
^{13}C NMR (D6-DMSO) δ 152.7 (d, J 240.4 Hz), 147.7 (d, J 147.7 Hz), 140.0, 134.9, 134.1 (d, J 10.3Hz), 133.8, 130.6, 128.8, 128.4, 118.9 (d 39 Hz), 54.5.

Example 4

2,3-Dichloro-*N*-[6-fluoro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]-benzenesulfonamide



a) Methyl 5-[[2,3-dichlorophenyl)sulfonyl]amino]-3-fluoro-6-methoxypyrazine-2-carboxylate



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N-(5-Bromo-6-fluoro-3-methoxypyraz-2-ynyl)-2,3-dichloro-benzenesulfonamide (product of example 3c) (0.4g) and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct (0.06g) in methanol (15ml) and triethylamine (5ml) was heated at 90-100°C under an atmosphere of carbon monoxide (6 bar). After 3h, the reaction was allowed to cool and the solution evaporated. The residue was partitioned between ethyl acetate and aqueous 2M hydrochloric acid. The aqueous layer was extracted with ethyl acetate and the combined extracts dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate. The solvent was evaporated to afford the product. Yield 0.25g.

m/e 410/412 (M+1)

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b) 2,3-Dichloro-*N*-[6-fluoro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]-benzenesulfonamide

Lithium triethylborohydride (Superhydride, 2ml of 1M solution in tetrahydrofuran) was added over 1 minute to a stirred solution of methyl 5-[[*N*-(2,3-dichlorophenyl)sulfonyl]-5-amino-3-fluoro-6-methoxypyrazine-2-carboxylate (product of step 4a) (0.17g) in dry tetrahydrofuran (5ml) cooled in an ice bath. After 20 minutes, the reaction mixture was partitioned between ethyl acetate and saturated aqueous citric acid. The combined ethyl acetate extract was washed with water, dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:1. The solvent was evaporated to afford the product. Yield 0.035g.

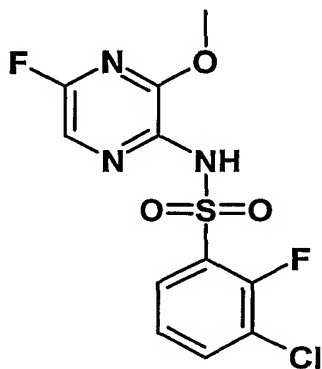
m/e 382/384/386 (M+1)

¹H NMR (D₆-DMSO) δ 8.11 (1H, dd), 7.95 (1H, dd), 7.61 (1H, t), 4.37 (2H, s) 3.91 (3H, s)

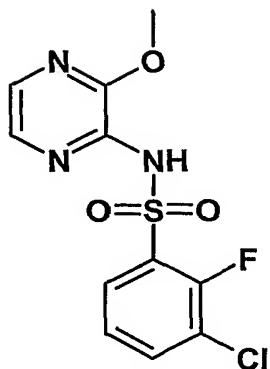
¹³C NMR (D₆-DMSO) δ 150.1 (d, J 241.1 Hz), 147.1 (d, J 2 Hz), 140.0, 134.9, 133.8, 132.8 (d, J 10.1 Hz), 130.9 (d, J 30.4 Hz), 130.6, 128.7, 128.4, 58.2, 54.5

Example 5

3-Chloro-2-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide



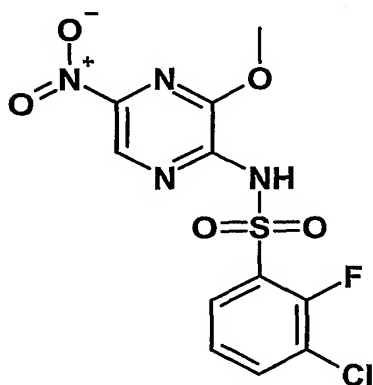
a) 3-Chloro-2-fluoro-*N*-(3-methoxypyrazin-2-yl)-benzenesulfonamide



Prepared by the method of example 1 step e using 3-chloro-2-fluorobenzenesulphonyl chloride (2.5g) and 3-methoxy-2-pyrazinamine (1.25g). After workup the combined ethyl acetate extracts were dried (MgSO₄) and evaporated to give a light brown solid. Yield 3.3g.

m/e 318/320 (M+1)

b) 3-Chloro-2-fluoro-N-(3-methoxy-5-nitropyrazin-2-yl)-benzenesulfonamide



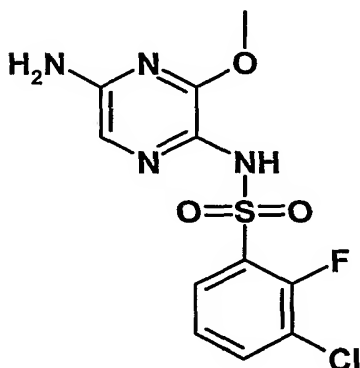
3-Chloro-2-fluoro-N-(3-methoxypyrazin-2-yl)-benzenesulfonamide (product of step 5a) (2.5g) was added to nitronium tetrafluoroborate in sulfolane (50ml of 0.5M solution) and the mixture heated at 50°C. After 6h, further nitronium tetrafluoroborate in sulfolane (20ml) was added. After a further 3h, the mixture was cooled and poured onto ice/water. The resulting oil was dissolved in ethyl acetate and separated. The combined ethyl acetate extracts were dried (MgSO₄) and evaporated to dryness to give an orange oil. Purification was by silica gel chromatography eluting with dichloromethane to remove the sulfolane

then ethyl acetate to collect the product. The product was dissolved in dichloromethane and washed with water to remove the residual sulfolane. The organic solution was dried (MgSO₄) and evaporated. Yield 1.2g.

¹H NMR (D₆-DMSO) δ 8.53 (1H, s), 7.95 (1H, t), 7.88 (1H, t), 7.42 (1H, t), 3.99 (3H, s)

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c) *N*-(5-Amino-3-methoxypyrazin-2-yl)-3-chloro-2-fluoro-benzenesulfonamide



3-Chloro-2-fluoro-*N*-(3-methoxy-5-nitropyrazin-2-yl)-benzenesulfonamide (product of step 5b) (0.8g), iron powder (0.8g) and ammonium chloride (0.8g) in ethanol (40ml) and water (40ml) was heated under reflux. After 1h, the reaction was allowed to cool and filtered through celite, washing well with methanol. The solution was evaporated to dryness then partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate. The solvent was evaporated to afford the product. Yield 0.28g.

¹H NMR (D₆-DMSO) δ 7.87 (1H, t), 7.67 (1H, t), 7.35 (1H, t), 7.11 (1H, s), 6.47 (2H, s), 3.58 (3H, s)

d) 3-Chloro-2-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide

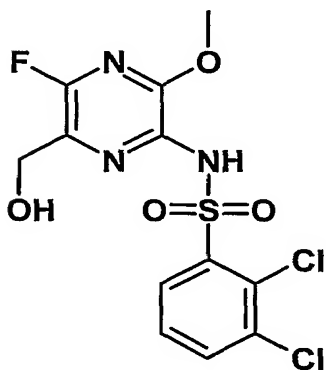
The title compound was prepared using the method of example 2 step c using *N*-(5-amino-3-methoxypyrazin-2-yl)-3-chloro-2-fluoro-benzenesulfonamide (product of step 5c) (0.27g). Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:3. The solvent was evaporated to afford the product. Yield 0.11g.

m/e 336/338 (M+1)

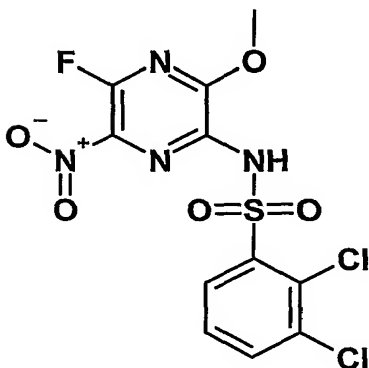
25

¹H NMR (D6-DMSO) δ 7.92 (1H, t), 7.86 (1H, t), 7.76 (1H, d), 7.43 (1H, t), 3.90 (3H, s)
¹³C NMR (D6-DMSO) δ 154.8 (d, J 249 Hz), 153.5 (d, J 258 Hz), 149.7 (d, J 9.1 Hz),
135.4, 133.9 (d, J 3.9 Hz), 130.7 (d, 13.4 Hz), 129.1, 125.5 (d, J 5.0 Hz), 121.1 (d, J 17.2
Hz), 118.1 (d, J 38.3 Hz), 54.7

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Example 6**2,3-Dichloro-*N*-[5-fluoro-6-(hydroxymethyl)-3-methoxypyrazin-2-yl]-benzenesulfonamide**

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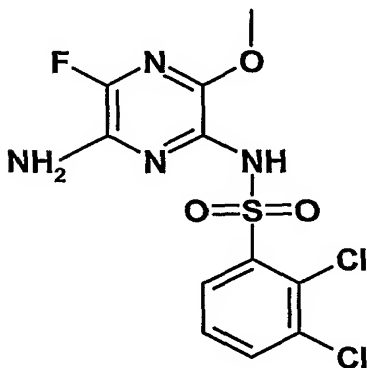
a) 2,3-Dichloro-*N*-(5-fluoro-3-methoxy-6-nitropyrazin-2-yl)-benzenesulfonamide

Nitronium tetrafluoroborate (0.4g) was added portionwise to a stirred suspension of
2,3-dichloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide (example 2) (0.5g)
in acetonitrile (10ml). After 2h, the reaction was partitioned between ethyl acetate and
water. The ethyl acetate extract was dried (MgSO₄) and evaporated. Purification was by
silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:1. The solvent was
evaporated to afford the product. Yield 0.3g.

15

¹H NMR (D6-DMSO) δ 8.25 (1H, dd), 7.94 (1H, dd), 7.61 (1H, t), 4.03 (3H, s)

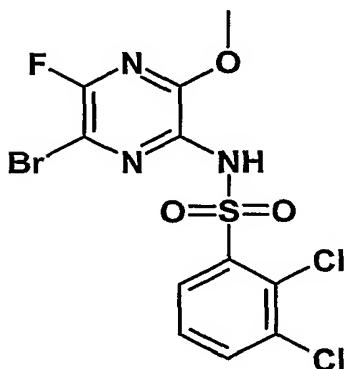
b) *N*-(6-Amino-5-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide



2,3-Dichloro-*N*-(5-fluoro-3-methoxy-6-nitropyrazin-2-yl)-benzenesulfonamide (product of step 6a) (0.95g) in ethyl acetate (10ml) and acetic acid (5ml) containing 5% palladium on charcoal (Johnson Matthey type 39 paste) (0.3g) was put under hydrogen (1 bar) with vigorous stirring. After 16h, the reaction mixture was filtered through a pad of celite and evaporated. Yield 0.75g.

m/s 367/369/371 (M+1)

c) *N*-(6-Bromo-5-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide

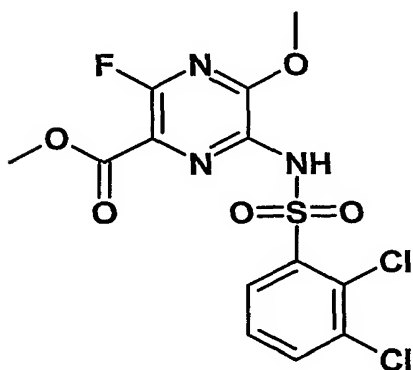


Sodium nitrite (0.2g) was added portionwise to a stirred solution of *N*-(6-Amino-5-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro-benzenesulfonamide (product from step 6b) (0.5g) in acetonitrile (5ml) and 48% aqueous HBr (5ml) cooled to -10°C . After 20 min, the reaction mixture was partitioned between dichloromethane and water. The organic extract

was dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with dichloromethane. The solvent was evaporated to afford the product. Yield 0.15g.

m/s 430/432 (M+1)

5 **d) Methyl 6-[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluoro-5-methoxypyrazine-2-carboxylate**



10 *N*-(6-Bromo-5-fluoro-3-methoxypyrazin-2-yl)-2,3-dichloro- benzenesulfonamide (product of example 6c) (0.14g) and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct (0.2g) in methanol (10ml) and triethylamine (5ml) was heated at 90-100°C under an atmosphere of carbon monoxide (6 bar). After 16h, the reaction was allowed to cool and the solution evaporated. The residue was partitioned between ethyl acetate and aqueous 2M hydrochloric acid. The aqueous layer was extracted
15 with ethyl acetate and the combined extracts dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:2. The solvent was evaporated to afford the product. Yield 0.1g.
m/e 410/412 (M+1)

20 **e) 2,3-Dichloro-*N*-[5-fluoro-6-(hydroxymethyl)-3-methoxypyrazinyl]-benzenesulfonamide**

Lithium triethylborohydride (Superhydride, 1.5ml of 1M solution in tetrahydrofuran) was added over 1 minute to a stirred solution of methyl 6-[(2,3-dichlorophenyl)sulfonyl]
25 amino}-3-fluoro-5-methoxypyrazine-2-carboxylate (product of step 6d) (0.1g) in dry

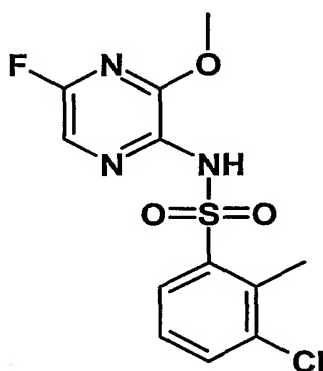
tetrahydrofuran (2ml) cooled in an ice bath. After 20 minutes, the reaction mixture was partitioned between ethyl acetate and aqueous 2M HCl. The combined ethyl acetate extract was washed with water, dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 2:1. The solvent was evaporated to afford the product. Yield 0.02g.

m/e 382/384/386 (M+1)

¹H NMR (D₆-DMSO) δ 11.49 (1H, br s), 8.10 (1H, dd), 7.94 (1H, dd), 7.59 (1H, t), 4.25 (2H, s), 3.85 (3H, s)

Example 7

3-Chloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-2-methyl-benzenesulfonamide



The title compound was prepared from 3-chloro-2-methylbenzenesulfonyl chloride (0.18g) and 5-fluoro-3-methoxy-2-pyrazinamine (product of example 2 step d) (0.1g) using the method of example 1 step e. Purification was by silica gel chromatography eluting with ethyl acetate:iso-hexanes 1:4. The solvent was evaporated to afford the product. Yield 0.15g.

¹H NMR (D₆-DMSO) δ 11.34 (1H, br s), 7.95 (1H, d), 7.73 (1H, d), 7.70 (1H, d), 7.43 (1H, t), 3.92 (3H, s), 2.66 (3H, s)

Pharmacological Data

FMAT Whole cell binding assay

Cells

CHO-K1 cells stably expressing the human recombinant CCR4 receptor (Euroscreen; Brussels, Belgium) were cultured in NUT.MIX.F_12(HAM) medium with glutamax-1, containing 10% (v/v) foetal bovine serum and 400 $\mu\text{g ml}^{-1}$ geneticin.

Cells were harvested at approximately 70% confluence by treatment with a cell dissociation buffer, and seeded at 5×10^3 cells/100 μl culture medium into wells of a black Costar clear-bottomed 96-well microtitre plates. Plates were incubated overnight at 37°C in 5% CO_2 and used the following day.

Assay

Before use, the cell plates were washed twice with 100 μl Hanks balanced salt solution (HBSS). To each well was then added 65 μl of HBSS, 10 μL of 10% DMSO in HBSS \pm test compound and then 25 μL of 2.8 nM FB-MDC (Applied Biosystems). This fluorescent probe was prepared from a 10 μM stock in 0.08% (v/v) TFA/16% (v/v) acetonitrile, diluted into HBSS.

After two hours incubation in the dark at room temperature, the plates were analysed in an FMAT8100 reader (Applied Biosystems) to measure fluorescence that was associated with binding of FB-MDC to the cells. Compound activity was determined as an pIC_{50} [-log(concentration of compound that results in 50% inhibition)], comparing fluorescence in control and background wells.

Measurement of Plasma Protein Binding

The extent of plasma protein binding was determined via equilibrium dialysis of a compound between human plasma and aqueous buffer at 37°C and determination of the concentration of compound in the plasma and buffer by HPLC-MS/MS.

Method

Dialysis cells (molecular weight cut-off 5000) were prepared by rinsing with water followed by soaking in the dialysis buffer for a minimum of 1 hour. The dialysis buffer was isotonic buffered saline pH 7.4. Stock solutions of compound in dimethylsulphoxide were prepared at a concentration of 1mM. Frozen pooled Human plasma was obtained from volunteers.

The stock DMSO solution of a compound was added to the plasma at a ratio of 10 μl of DMSO to each ml of plasma. This gave a 1% DMSO in plasma solution with each compound at a concentration of 10 μM .

Dialysis cells were then prepared and one half of the cell filled with 750 µl of dialysis buffer and the other half of the cell with 750 µl of plasma solution of compound. Once prepared the cells were sealed and immersed in a water bath at 37°C. These cells were then rotated for a minimum of 4 hours to equilibrate.

After equilibration 500 µl of the buffer samples were removed and added to HPLC vials along with 100 µl of plasma (sample in 6-fold diluted plasma), and 100 µl of the plasma samples were removed and added to HPLC vials along with 500 µl of dialysis buffer (sample in 6-fold diluted plasma).

The samples were then analysed using HPLC-MS/MS. A four point calibration curve was obtained by dilutions of the stock solutions with 6-fold diluted plasma at concentrations of 0.05 µM, 0.15 µM, 0.5 µM and 2.5 µM which were injected in this order followed by the buffer sample and then the plasma sample.

Calculation

The concentration of compound in the samples were determined using MassLynx version 4.0 software (produced by Waters/Micromass) that automatically calculated a calibration curve and the concentration of compound in the cells. Plasma protein binding was determined from the calibration curve as the percentage of compound bound in human plasma (% bound) using the following equation wherein the factor in the numerator accounts for the small dilution of the aqueous samples with plasma and the factor of 6 in the denominator serves to correct for the 6-fold dilution of the plasma samples with buffer;

$$\% \text{bound} = 100 - 100 \left(\frac{1.2 \left(\frac{\text{Buffer concentration} \times \text{Standard Injection vol.}}{\text{Buffer injection vol.}} \right)}{6 \left(\frac{\text{Plasma concentration} \times \text{Standard injection vol.}}{\text{Plasma injection vol.}} \right)} \right)$$

Whole Blood Potency

Predicted whole blood potency is a measure of the combined effects of CCR4 activity and plasma protein binding, and is calculated by the formula: Whole Blood Potency = CCR4 pIC50 + Log ((100- %Bound)/100).

Results

Table 1 shows the CCR4 pIC₅₀, plasma protein binding (%bound) figures and predicted whole blood potency for Examples 1-7 according to the present invention and comparative compounds from WO03/059893. The comparative compounds are the analogous chlorine-containing and bromine-containing compounds exemplified in WO03/059893 (Example 5, 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide; and Example 8, 2,3-dichloro-N-(5-bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide) and Example 30 (2,3-dichloro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide).

Table 1

Compound of Example No.	FMAT CCR4 pIC ₅₀	% Bound Human Plasma	Whole Blood Potency
1	8.3	99.0	6.3
2	8.5	99.4	6.3
3	8.5	99.7	6.0
4	7.8	98.7	5.9
5	8.0	98.9	6.0
6	8.2	99.5	5.9
7	8.4	99.6	6.0
Ex. 5 WO03/059893	7.9	99.8	5.2
Ex. 8 WO03/059893	8.3	99.8	5.6
Ex. 30 WO03/059893	7.7	98.9	5.7

The whole blood potency of the compounds of the present invention, wherein the pyrazine ring is substituted with fluorine in the 5 or 6 positions, is significantly higher than

for the comparative compounds wherein the pyrazine is substituted with chlorine or bromine. The combination of very high potency and low plasma protein binding to human plasma makes the fluorine-containing compounds of the present invention more efficacious in vivo.

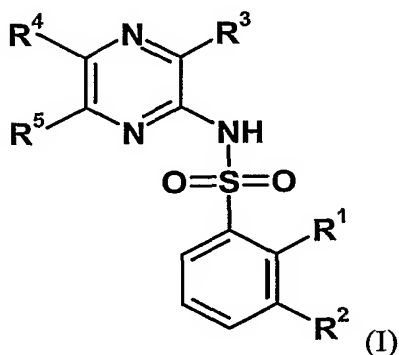
Metabolite Testing

5-Fluoro-3-methoxy-2-pyrazinamine and 6-fluoro-3-methoxy-2-pyrazinamine were tested for mutagenicity according to the test procedure of Maron and Ames described in Mutation Res. 1983; 113:173-215 using *salmonella typhimurium* LT2 strains TA98 and TA100. For metabolic activation a homogenate of liver from Aroclor 1254-treated rats (post-mitochondrial fraction (S9) purchased from Molecular Toxicology Inc., Boone, North Carolina, USA) was added to agar plates (without histidine) together with the test compound and the bacterial tester strains; the complete activation system employed was: phosphate buffer (0.1 mol/L, pH 7.4):100 mmol/L; magnesium chloride: 8 mmol/L; potassium chloride: 33 mmol/L; nicotinamide adenine dinucleotide phosphate: 4 mmol/L; glucose-6-phosphate:5 mmol/L; and rat liver homogenate (S9 fraction):10 % v/v. The mean number of revertant colonies and sample standard deviation (from control plates) were calculated for each test group. A test compound was considered to be mutagenic when the following criteria were satisfied: i) the number of revertant colonies in any strain increased in the presence of one or more dose of the test compound, with or without metabolic activation ii) there was a dose-related increase in the number of revertant colonies, and iii) any increase was reproducible.

For both 5-fluoro-3-methoxy-2-pyrazinamine and 6-fluoro-3-methoxy-2-pyrazinamine the test result was negative indicating the compounds are not mutagenic in the test conditions.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R¹ is selected from methyl, chlorine and fluorine;

R² is selected from methyl, chlorine and fluorine;

R³ is methoxy;

one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is selected from hydrogen and hydroxymethyl.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from chlorine and fluorine, and R² is selected from chlorine and fluorine.

3. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R⁴ is fluorine and R⁵ is selected from hydrogen and hydroxymethyl.

4. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R⁵ is fluorine and R⁴ is selected from hydrogen and hydroxymethyl.

5. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is hydrogen.

6. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein one of R⁴ and R⁵ is fluorine and the other of R⁴ and R⁵ is hydroxymethyl.

7. A compound according to claim 1, which is selected from

5 2-Chloro-3-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-(6-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-[6-fluoro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]-
benzenesulfonamide,

10 3-Chloro-2-fluoro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-benzenesulfonamide,

2,3-Dichloro-*N*-[5-fluoro-6-(hydroxymethyl)-3-methoxypyrazin-2-yl]-
benzenesulfonamide,

3-Chloro-*N*-(5-fluoro-3-methoxypyrazin-2-yl)-2-methyl-benzenesulfonamide
or a pharmaceutically acceptable salt thereof.

15 8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

20 9. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7 for use in therapy.

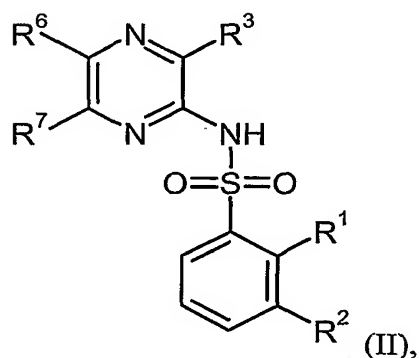
10. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as
claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in the
25 treatment of asthma.

11. A method of treating a disease mediated by the CCR4 receptor, which comprises
administering to a patient a therapeutically effective amount of a compound of formula (I),
or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7.

12. A method of treating asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7.

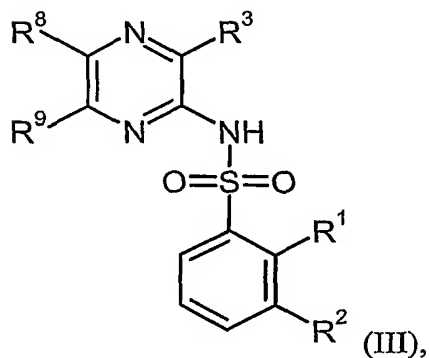
13. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises

(a) reacting a compound of formula (II), wherein R^1 , R^2 and R^3 are as defined in formula (I) and one of R^6 and R^7 is hydrogen and the other of R^6 and R^7 is NH_2 , with a nitrite salt in the presence of a fluorinating agent,



or

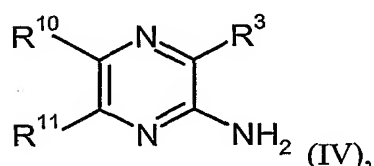
(b) reacting a compound of formula (III), wherein R^1 , R^2 and R^3 are as defined in formula (I) and one of R^8 and R^9 is fluorine and the other of R^8 and R^9 is bromine, with hydrogen in the presence of a palladium catalyst,



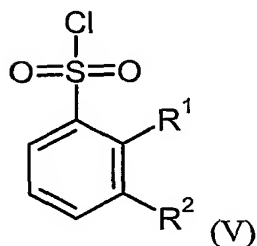
or

(c) where one of R^4 and R^5 is hydroxymethyl, reacting a compound of formula (III) as described in (b), with carbon monoxide in the presence of a palladium catalyst, and subsequently treating the resulting acid (or C_{1-4} alkyl ester thereof) with a suitable reducing agent, or

- 5 (d) where one of R^4 and R^5 is fluorine and the other of R^4 and R^5 is hydrogen, reacting a compound of formula (IV), wherein R^3 is as defined in formula (I) and where one of R^{10} and R^{11} is fluorine and the other of R^{10} and R^{11} is hydrogen,

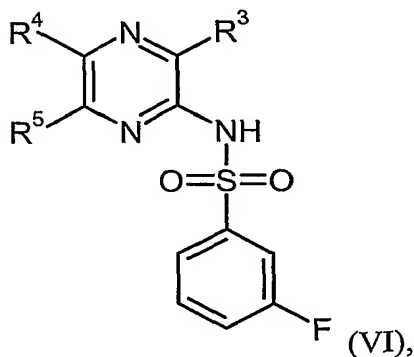


- 10 with a compound of formula (V), wherein R^1 and R^2 are as defined in formula (I)



or

- (e) where R^2 is fluorine and R^1 is chlorine, reacting a compound of formula (VI) wherein
 15 R^3 , R^4 and R^5 are as defined in formula (I), with hexachloroethane in the presence of a lithium amide or alkyl lithium base,



and optionally after (a), (b), (c), (d) or (e) carrying out one or more of the following:

- converting the compound to a further compound of the invention or
- forming a pharmaceutically acceptable salt of the compound.

5 14. A compound of formula (IV),



wherein R³ is methoxy; one of R¹⁰ and R¹¹ is fluorine and the other of R¹⁰ and R¹¹ is hydrogen.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-12
because they relate to subject matter not required to be searched by this Authority, namely:
claims 11-12 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic
.../...
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The following separate inventions were identified:

- 1: Claims 1-13 directed to a compound of formula (I).
- 2: Claim 14 directed to intermediates of formula (IV).

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/001409

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03059893 A1 (ASTRAZENECA AB), 24 July 2003 (24.07.2003) --	1-14
A	WO 2004108692 A1 (ASTRAZENECA AB), 16 December 2004 (16.12.2004) --	1-13
A	WO 03004472 A1 (ASTRAZENECA), 16 January 2003 (16.01.2003) --	1-13
A	WO 2004108717 A1 (ASTRAZENECA AB), 16 December 2004 (16.12.2004) --	1-14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 April 2007

Date of mailing of the international search report

02 -05- 2007

Name and mailing address of the ISA/
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/001409

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005021513 A1 (ASTRAZENECA AB), 10 March 2005 (10.03.2005) --	1-13
A	GB 928151 A (CAMERINO, BRUNO ET AL), 6 June 1963 (06.06.1963) -- -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001409

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

International patent classification (IPC)**C07D 241/22** (2006.01)**A61K 31/4965** (2006.01)**A61P 11/00** (2006.01)**A61P 11/06** (2006.01)**Download your patent documents at www.prv.se**

The cited patent documents can be downloaded at www.prv.se by following the links:

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Use the application number as username.

The password is **UAZUAGYXAC**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/03/2007

International application No.

PCT/SE2006/001409

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INTERNATIONAL SEARCH REPORT
Information on patent family members

31/03/2007

International application No.
PCT/SE2006/001409

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